66. The isolated HPV L1 protein of claim 64, which is selected from the group consisting of HPV-11, HPV-16 and HPV-18.--

REMARKS

Entry of the foregoing amendments, reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendments, Claims 1, 12, 19, 50 and 63 have been amended to expedite prosecution. In particular, the phrase "intact, native human papillomavirus virions" has been changed to "intact human papillomavirus virions". Further, in accordance with a suggestion made by the Examiner at the recent personal interview, Claims 1, 12, 19, 50 and 63 have been amended to recite that the recombinantly produced HPV L1 protein is isolated. Also, in Claim 63, the phrase "intact, mature human papillomavirus virions" has been changed to "intact human papillomavirus virions". Also, new Claims 64-66 are added. Upon entry of the present amendments, Claims 1-3, 10-19, 21-26, 46, 47, 50 and 63-66 will remain pending. Support for the amendatory claim language may be found, e.g., at page 10, lines 1-12 of the as-filed application.

At the outset, the Examiner is thanked for the recent personal interview held on July 11, 1996, with Examiner Caputa, Examiner Mosher, Jim Young and Kai Chen, representatives of MedImmune, Inc., the licensee of this application, Carol L. Tracy, a representative of Georgetown University, the Assignee,

Danny Huntington, and the undersigned. During the interview, the outstanding rejections were discussed in view of a proposed Response submitted to the Examiner on July 10, 1996.

Examiners Mosher and Caputa advised that based on their review of the proposed Response, and the amended claims, that the §102 and §103 rejections based on Carter et al, alone, or in view of Danos et al, would be vacated if the independent claims were amended to recite that the recombinantly produced HPV L1 protein is "isolated". The Examiners acknowledged that neither Carter et al or Danos et al teaches or suggests an isolated HPV L1 protein having the recited properties (conformation which mimics that of an L1 protein expressed on the surface of an intact HPV virion).

Also, the §112 new matter rejection was discussed. The Examiners advised that this rejection would be withdrawn based on the proposed amendments.

Finally, the §112 enablement rejection with respect to the asserted non-enablement of HPV-16 was discussed. Essentially, Applicants explained the generic nature of the claimed invention, and argued that the specification provides enough information for one skilled in the art to produce any desired HPV L1 protein which reproduces the conformation of L1 proteins expressed on the surface of the corresponding intact HPV virions. With respect to HPV-16 in particular, it was argued that one skilled in the art could readily isolate HPV-16 L1 DNA from a suitable cellular source, e.g., cells of a premalignant cervical lesion, express such DNA, and determine with conformational monoclonal antibodies whether the expression product exhibits the appropriate conforma-

tion. Applicants further explained that a suitable cellular source for obtaining an HPV-16 L1 DNA which would have been known at the time of invention is cells comprised in premalignant cervical lesions or cervical warts. It was noted that HPV-16 exists in episomal form in such cells (rather than integrated into the cellular genome) and therefore the HPV-16 viral DNA would not be expected to have mutated. By contrast, it was explained that HPV-16 is subject to mutation upon integration.

In response to such arguments at the interview, the Examiners advised that they would vacate the §112 enablement rejection with respect to HPV-16 if evidence were submitted establishing that a suitable source of HPV-16 particles was known at the time of invention. Examiner Mosher explained that such evidence is necessary to rebut the rejection because such particles would be required to produce conformational monoclonal antibodies specific to HPV-16 L1 protein which are necessary for use in the disclosed screening process (to determine whether expressed HPV L1 protein exhibits appropriate conformation). Accordingly, Applicants submit herewith several references which disclose cellular sources which were known at the time of invention to contain HPV-16 particles.

Also, Applicants further attach to this Reply a schematic which outlines another assay for determining whether an expressed HPV-16 L1 protein exhibits appropriate conformation (which assay does not require purified HPV-16 particles). While this assay is not explicitly identified in the application, it would have been routine to one skilled in the art based on the information con-

tained in this application and the known type-specificity of HPV conformational antibodies.

Therefore, based on this additional evidence, and for the reasons set forth *infra*, it is believed that this Reply should place this case in condition for allowance.

Turning now to the Office Action, the Examiner's withdrawal of numerous of the previous prior art rejections is acknowledged. The only remaining prior art rejections from the previous Office Action are the rejections of Claims 1-3, 10, 12, 15, and 59-62 based on Carter et al (*Virology*, 182, 513-521 (1991)), and of Claims 16, 23, 24, 52 and 55 to 63 based on Carter et al in view of Danos et al. However, as discussed above, this rejection is to be withdrawn based on the present amendments.

The Office Action maintains that these claims are anticipated, or in the alternative, rendered obvious by Carter et al, alone or in combination with Danos et al.

This rejection is only applied against the claims which embrace HPV-1 L1 proteins which reproduce the antigenicity and exhibit the same conformation as intact human papillomavirus virions. Essentially, the Office Action indicates that it is reasonable to conclude that the HPV-1 L1 proteins obtained by Carter et al, which were expressed in *Saccharomyces cerevisiae* would "inherently" mimic the conformation of an L1 protein expressed on the surface of intact HPV-1 virions. The Office Action substantiates this position by reliance on the fact that these proteins are disclosed by Carter et al to possess the expected molecular weight of native HPV-1 L1 protein and also

based on the fact that these proteins apparently bind to monoclonal antibodies specific to HPV-1 L1 protein.

However, Applicants respectfully submit that neither of these facts substantiates a reasonable conclusion that the HPV-1 L1 protein obtained by Carter et al exhibits "appropriate conformation". By "appropriate conformation", Applicants refer to an L1 protein which exhibits the same conformation as an L1 protein expressed by intact HPV virions, e.g., HPV-1 virions. Thus, the HPV-1 L1 protein of Carter et al must contain the same conformational epitopes as an HPV-1 L1 protein expressed on the surface of intact HPV-1 virions to have "appropriate conformation". Based on the following, the anticipatory rejection must be withdrawn because Carter et al contains no evidence which would allow one skilled in the art to reasonably conclude that their HPV-1 L1 proteins were of appropriate conformation.

The first property, i.e., molecular weight, merely suggests that whatever HPV-1 L1 sequence cloned by Carter et al was apparently transcribed, translated and the L1 protein was not substantially degraded. However, it is otherwise irrelevant because molecular weight cannot be used to determine whether a protein exhibits a particular conformation.

The second property, i.e., the reactivity of the HPV-1 L1 proteins of Carter et al with monoclonal antibodies further does not substantiate a conclusion that these L1 proteins exhibit a conformation characteristic of intact HPV virions. This is because Carter et al tested the immunoreactivity of their L1 proteins with monoclonal antibodies which bind to linear epi-

topes. This deficiency of Carter et al is discussed in the most recent Declaration by Dr. Schlegel and Dr. Jenson (dated October 24, 1995) (hereinafter the Schlegel and Jenson §132 Declaration). Therein, the Declarants further note that L1 proteins which exhibit appropriate conformation (conformation characteristic of native, intact HPV-1 L1 proteins) can only be assessed based on their reactivity with conformationally-dependent antibodies. [*See* paragraph 7 of Schlegel and Jenson §132 Declaration.] Thus, contrary to the Office Action, Carter et al contains no evidence which would allow one skilled in the art to reasonably conclude that their HPV-1 L1 proteins expressed intracellularly in yeast exhibit appropriate conformation.

Moreover, Applicants respectfully maintain that there is sufficient evidence of record to establish that Carter et al would not have obtained HPV-1 L1 proteins having appropriate conformation. For example, the fact that Carter et al. cloned their HPV-1 L1 sequence by polymerase chain reaction (PCR), a cloning technique which is well known to introduce mutation(s), (on average this technique introduces 3-5 nucleotide errors for a nucleotide sequence which is about 1500 nucleotides) substantiates Applicants' position that the HPV-1 L1 sequence expressed by Carter et al would be expected not to possess appropriate conformation, i.e., the conformation of native HPV-1 L1 proteins.

This argument finds factual support in the same §132 Declaration of Dr. Schlegel and Dr. Jenson. Notwithstanding this Declaration evidence, the §102(b)/§103 inherency rejection based on Carter et al has been maintained. Essentially, the Examiner

reasons that while PCR typically introduces mutations, and that it would be therefore reasonable to assume that the L1 sequence cloned by Carter et al likely contained one or more mutations, that there is no reason to conclude that any of these mutations would have affected conformation. The Examiner notes that such mutations could have been silent (not affect amino acid sequence), or alternatively, even if they altered the primary amino acid sequence, such changes may not cause significant affects on the conformation of the resultant HPV-1 L1 protein.

However, this conclusion is respectfully traversed. While Applicants acknowledge that some mutations introduced into the HPV-1 L1 sequence would reasonably be expected to exert no effect on conformation of the resultant expressed protein, given the inherent sensitivity of HPV-1 L1 to conformational changes (as evidenced by the drastic effects of a single amino acid change in the HPV-16 L1 sequence), it would be reasonable to conclude that at least one of the expected 3 to 5 mutations in the L1 sequence expressed by Carter et al would have altered the conformation of the resultant HPV-1 L1 protein.

Applicants respectfully note that the initial burden to substantiate an inherency based §102 or §103 rejection is on the Patent Office. (*See*, In re Piasecki, 223 U.S.P.Q. 785 (CAFC 1984). Moreover, inherency must be certain. Ex parte Cyba, 158 U.S.P.Q. 756 (POBA 1966). Essentially, it must be a necessary result and not merely a possible result. Ex parte Keith et al, 154 U.S.P.Q. 320 (POBA 1966). Only after this initial burden has been met, does the burden then shift to Applicant to rebut the

inherency based rejection. In re Murch, 175 U.S.P.Q. 89 (CCPA 1972).

However, based on the evidence of record, Applicants respectfully submit that a proper inherency based rejection has not been set forth, essentially because there is no evidence which would allow one skilled in the art to reasonably conclude that the HPV-1 L1 proteins expressed by Carter et al reproduced the antigenicity and conformation of an HPV-1 L1 protein expressed by intact, infectious HPV-1 virions.

Moreover, there is yet even further reason to reasonably conclude that the HPV-1 L1 proteins expressed by Carter et al. could not have exhibited proper conformation. In particular, Applicants note that the HPV-1 L1 proteins of Carter et al were expressed in intracellular form in *Saccharomyces cerevisiae* and then released therefrom by pelleting the yeast, washing, and disruption by mechanical lysis using glass beads in a buffer containing Tris, EDTA, sodium dodecyl sulfate (SDS), and Triton X-100. (*See* left-hand column, page 515 of Carter et al, lines 4-8.) However, it is well known that SDS is a strong denaturant. In fact, SDS is conventionally used to provide for unfolding of proteins. (*See* page 174 of *Mol. Biol. of the Cell*, Alberts et al, Eds. 1983, attached to this Reply.) Therefore, given the usage of SDS during HPV-1 L1 protein recovery, it is reasonable to conclude that any HPV-1 L1 proteins which were contained in the yeast lysate material disclosed by Carter et al would not exhibit the same conformation as an L1 major capsid protein expressed on the surface of intact human papillomavirus virions.

Rather, it would be expected that conformational epitopes would not be expressed because of the known denaturing effects of SDS.

The fact that SDS has denaturing effects on recombinant PV L1 proteins is further substantiated by Suzich et al, *Proc. Natl. Acad. Sci. USA*, 92:11553-11557 (1995), which discloses the use of SDS-denatured COPV L1 VLPS as a negative control to confirm that (unlike conformational L1 proteins), denatured PV L1 proteins do not confer immunoprotection. *See*, in particular, the results in Table 1 at page 11555 of Suzich et al (*Id.*) which indicate that SDS-denatured COPV L1 VLPS conferred no protection, whereas conformationally intact recombinant COPV L1 VLPS conferred protection in all animals immunized.

Also, the denaturing effects of SDS on PV proteins is further substantiated by Kirnbauer et al, *Proc. Natl. Acad. Sci. USA*, 89:12180-12184 (1992). *See* Table 1, at page 12183, wherein Kirnbauer et al disclosed that SDS treated HPV-L1 proteins do not elicit neutralizing antibodies, unlike intact BPV-1 L1 virions (native or recombinant). Thus, the denaturing effects of SDS on PV L1 proteins is recognized in the art.

Moreover, the §102/103 inherency rejection is separately argued as it is applied to Claims 12 and 15. These claims are directed to a vaccine suitable for the prevention of human papillomavirus infection, which comprises at least one recombinantly produced human papillomavirus virions (PV) L1 protein, which protein reproduces the antigenicity and exhibits the same conformation as an L1 major capsid protein expressed on the surface of intact, infectious human papillomavirus virions.

There is absolutely no basis for concluding that Carter et al teaches or suggests a composition containing HPV-1 L1 proteins which would be suitable for use as a vaccine for the prevention of papillomavirus infection. In fact, the reference contains no teaching or suggestion concerning the use of their disclosed HPV-1 L1 proteins, or any of their expressed HPV proteins, for use in vaccines. Rather, the only prophetic usage of the disclosed recombinant HPV proteins is for examining humoral immunity to papillomaviruses, and for the study of cellular immunity and for structure/function studies of the proteins themselves. (*See*, page 520, last paragraph, preceding "Acknowledgements", of Carter et al.) Therefore, based on the foregoing, and as agreed to at the recent personal interview, withdrawal of the §102(b)/103 rejection of Claims 1-3, 10, 12, 15 and 59-62 based on Carter et al. is respectfully requested.

Claims 13, 14, 18, 19, 21, 25, 46, 47, 50, 51, 53, 54, and 59-62 further stand rejected under 35 U.S.C. §103 as being unpatentable over Carter et al. as applied to Claims 1-3, 10, 12, 15, and 59-62 and further in view of Danos et al (U. S. Patent No. 4,551,270). Essentially, the Examiner asserts that Carter et al discloses an HPV-1 L1 protein expressed in yeast which, absent evidence to the contrary, would appear to exhibit the conformation of HPV-1 L1 proteins expressed by intact HPV-1, and that in view of Danos et al it would have been obvious to have used such proteins as a vaccine for conferring immunity against HPV-1 infection. This rejection is not made against the claims which do not encompass the use of HPV-1 L1 protein as a vaccine.

For the reasons set forth above, Carter et al does not teach or suggest an HPV-1 L1 protein which would exhibit the conformation of L1 proteins expressed on the surface of intact HPV-1 virions. Nor does the reference teach or suggest the use of their HPV-1 L1 proteins as vaccines. Rather, the reference teaches the expression of HPV proteins which are assertedly useful for diagnostic use.

The addition of Danos et al does not compensate for the deficiencies of Carter et al. As acknowledged by the Examiner, this reference teaches linear peptides which purportedly are useful in the preparation of HPV vaccines. However, as previously argued, these peptides would be unsuitable for use in vaccines because linear peptides do not confer immunity against HPV infection. Rather, proper conformation is essential for a protective immune response. The Office Action indicates that Applicants have failed to indicate where in the record or in the art it had been previously established that linear HPV-1 proteins and peptides are not useful as vaccines. Also, the Office Action indicates that this argument is unpersuasive because issued patents are presumed valid.

However, Applicants respectfully note that the as-filed application specifically discloses that linear molecules corresponding to the L1 protein are incapable of protecting against papillomavirus infection, whereas conformationally correct L1 proteins (produced by the subject invention) are capable of inducing neutralizing antibodies which protect against papillomavirus infection. (*See*, e.g., page 8, lines 8-13, of the as-filed

specification.) Indeed, this is the crux of the present invention. With respect to HPV-1 in particular, the application specifically teaches expression of HPV-1 L1 proteins in Cos cells and contains evidence which demonstrates that the resultant recombinant HPV-1 L1 proteins specifically bind to monoclonal antibodies that recognize conformational epitopes expressed on the surface of HPV-1 particles.

The fact that appropriate L1 conformation is essential for an effective HPV vaccine, i.e. one that protects hosts against infection by the corresponding human papillomavirus virus, is further substantiated by the §132 Declaration dated June 10, 1994, by Dr. Schlegel. This Declaration contains experiments which provide *in vivo* evidence that conformationally correct papillomavirus proteins confer immunity against papillomavirus infection in susceptible animals. These experiments utilize the COPV/canine animal model. As previously established, COPV is an accepted *in vivo* model for HPV.

In particular, the results described at pages 13-14 of the Declaration, provide conclusive evidence substantiating the importance, i.e., essentiality, that an L1 protein must appropriate conformation to confer protective immunity, and that linear epitopes are apparently not involved in conferring protection against PV infection. Specifically, these results indicate that Beagle dogs which were inoculated with recombinant conformationally correct COPV L1 produced a substantial antibody response against COPV conformational epitopes. By contrast, the control group (which were not administered these proteins) exhibited

virtually no change in the antibody response to conformational epitopes after challenge.

Moreover, while vaccinated animals developed an immune response to conformational L1 proteins, they failed to develop a significant response to linear, i.e. non-conformational epitopes. This may be appreciated upon review of the results contained in Figure 3 of the Schlegel Declaration. Therefore, these results demonstrate that antibodies to linear epitopes (such as would be obtained upon administration of the HPV-1 L1 proteins of Danos et al) do not confer protection. Based on the fact that COPV is an acceptable model for mucosotropic PV's, including HPV's which cause oral and cervical warts and cancers, it is reasonable to conclude, based on these results, that linear peptides derived from HPV-L1 could not be used to confer protection against HPV-1 infection. Moreover, these results demonstrate that linear and conformational HPV L1 sequences do not function equivalently.

Also, the essentiality of appropriate conformation to an effective immune response is substantiated by Suzich et al, *Proc. Natl. Acad. Sci. USA*, 92:11553-11557 (1995), as well as Kirnbauer et al, *Proc. Natl. Acad. Sci. USA*, 89:12180-12184 (1992), both discussed above.

Moreover, there are numerous references of record which substantiate the overwhelming acceptance by those skilled in the art that the presentation of conformational L1 epitopes is essential for eliciting a protective immune response against papillomavirus virus infection. *See*, e.g., *Gynecological Oncology*, 55:10-12 (1994), entitled "Recombinant Virus-Like Particles

Retain Conformational Epitopes of Native Human Papillomaviruses and May be Useful for Vaccine Development"). *See* also, Heins et al, *Gynecological Oncology*, 55:13-20, (1994), entitled "Role of Conformational Epitopes Expressed by Human Papillomavirus Major Capsid Proteins in the Serologic Detection of Infection and Prophylactic Vaccination".

Therefore, contrary to the Office Action, Applicants respectfully submit that there is substantial evidence of record which demonstrates the importance, i.e. essentiality, of conformational L1 epitopes for eliciting protection against papillomavirus virus infection. Therefore, based on the foregoing, and as agreed to at the recent personal interview (based on the subject amendments), withdrawal of the §103 rejection of Claims 13, 14, 18, 19, 21, 25, 46, 47, 50, 51, 53, 54 and 59-62 under 35 U.S.C. §103 based on Carter et al taken in view of Danos et al is respectfully requested.

Claims 10, 11, 15, 17, 18, 21, 22, 26, 51, 54 and 63 stand newly rejected under 35 U.S.C. §112, first paragraph, as being non-enabled. Essentially, the Office Action asserts that the specification fails to enable synthesis of an HPV-16 L1 protein which reproduces the antigenicity and conformation of L1 proteins expressed by native, intact HPV-16 virions. The Examiner, however, acknowledged at the interview that the generic claims are free of this rejection. The Examiner indicates that these claims are not enabled because the HPV-16 L1 sequence which was publicly known contained a mutation which upon expression resulted in a HPV-16 L1 protein which does not exhibit proper conformation,

i.e. does not reproduce the antigenicity and conformation of a HPV-16 L1 protein expressed on the surface of intact, infectious HPV-16 virions. This rejection is respectfully traversed.

While it is acknowledged that the HPV-16 L1 sequence which had been widely reported (HPV-16 L1 sequence represented by Zur Hausen) contained a mutation which adversely affects conformation, Applicants respectfully submit that the as-filed application contains enough information to enable the production of HPV-16 L1 proteins exhibiting appropriate conformation. Specifically, once it had been established that HPV sequences could be expressed having appropriate conformation (as disclosed in the subject application), it would have been well within the level of ordinary skill to clone an HPV-L1 sequence from <u>any</u> infectious human papillomavirus (including HPV-16) and to express such L1 sequence according to the teachings of the application in order to obtain the corresponding conformational HPV L1 protein.

Moreover, with particular respect to HPV-16, it had been well known in the art at the time of invention that HPV-16 DNA is frequently detected in cervical warts and premalignant cervical lesions. (*See*, Bubb et al, *Virology*, 163:243-246 (1988), attached to this Reply). In fact, this reference exploits this fact by isolating an infectious form of HPV-16 from extra chromosomal viral DNA contained within a premalignant cervical lesion.

Therefore, based on what had been known in the art at the time of invention, one skilled in the art, in possession of this application, could, absent undue experimentation, clone an infectious form of HPV-16 (e.g., from a premalignant cervical tumor),

isolate the HPV-16 L1 sequence therefrom, and express the L1 sequence using the teachings of this application in order to produce a conformational HPV-16 L1 protein. Moreover, whether the resultant protein exhibits appropriate conformation could readily be determined based on whether this HPV-16 L1 protein reacts with conformational antibodies specific to HPV-16 L1 proteins.

Also, the isolation of HPV-16 L1 DNA from cervical warts or premalignant cervical lesions further would have been obvious based on Bubb et al, (*Id.*) who disclose that HPV-16 is prone to mutation after after integration into the cellular genome. This reference explains that such mutation may occur in order to "turn off" viral genes and thereby protect the virus from the host immune system. (*See* page 295, right-hand column of Bubb et al (*Id.*).)

Still another reason for isolating HPV-16 L1 DNA from such cellular sources, rather than using the sequence of Zur Hausen et al is the fact that Bubb et al (*Id.*) disclose that the published HPV-16 sequence of Zur Hausen (which was sequenced by Seedorf et al) (*Virology*, 145:181-185 (1985)) contains at least one error in the HPV-16 E5 Sequence which results in a frame shift mutation in the E5 gene. (*See* page 243 of Bubb et al (*Id.*).)

Based on similar arguments, the Examiner advised at the recent interview that the enablement rejection with respect to HPV-16 would be reconsidered, and would likely be withdrawn, upon submission of convincing evidence that suitable sources of HPV-16 particles were known and available at the time of invention. The

Examiner indicated that such particles would be necessary (as an immunogen) in order to produce conformational monoclonal antibodies against L1 proteins expressed on the surface of intact HPV-16 virions (to be used in the disclosed screening process).

Therefore, Applicants provide herewith several references which disclose suitable cellular sources of HPV-16 L1 particles, which were known and widely available in the art at the time of invention. First, Applicants note that a keratinocyte cell line which produces intact HPV-16 virions was publicly known and available at the time of invention. (*See* Sterling et al, *J. Virol.*, 64(12):6305-6307 (1990), attached to this Reply). Applicants note that consistent with wild-type HPV-16 virions, the virions expressed by this cell line are about 50 nm in diameter. Therefore, this cell line provides a continuous source of HPV-16 virions which can be used for monoclonal antibody production. Applicants further advise that this cell line was in the public domain at least as of 1990, as required for any cell line disclosed in *The Journal of Virology*, a highly respected journal in virological research.

Also, it had been well reported in the literature prior to the filing date of this application that HPV-16 particles may be visualized by electron microscopy in the nucleus of specific cell types, e.g., Koilocytotic cells contained in precancerous cervical lesions. (*See*, Kadish et al, *Human Pathol.*, 17(4):384-392 (1986); Syrjanen et al, *Eur. J. Gynaec. Oncol.*, Vol. VIII(i):5-16 (1987); Tsutsumi et al, *Acta Pathol. Japonica*, 41(10):757-762 (1991); and Chang et al, *Scand. J. Gastroentol.*, 27:553-563

(1992), attached to this Reply.) Therefore, cellular sources suitable for obtaining HPV-16 particles were known at the time of invention.

Also, at the time of invention, methods for using HPV virion containing tissues as immunogens for producing antisera, and for immunological staining were also known. (*See*, Jenson et al, *Lab Invest.*, Vol. 47(5):491-497 (1982); Jenson et al, *Amer. J. Pathol.*, 107:212-218 (1982); and Jenson et al, *JNCI.*, Vol. 64(3):495-500 (1980) attached to this Reply).

Therefore, the foregoing references demonstrate that suitable cellular sources of HPV-16 virions and methods for producing antibodies specific thereto were known and available at the time of invention.

Also, Applicants respectfully advise that there is yet another method for confirming whether an expressed HPV L1 protein exhibits appropriate conformation. This method, which is outlined schematically as an attachment to this Reply, involves obtaining an HPV-16 L1 sequence from a suitable cellular source, e.g., a premalignant cervical lesion, expressing such L1 sequence according to the invention, producing antibodies thereto, and then ascertaining whether such antibodies are type-specific. Essentially, if the resultant antibodies are type-specific, that is, only react with HPV-16 virions, and fail to react with denatured HPV-16 virions, then the protein exhibits appropriate conformation. By contrast, if the resultant monoclonal antibodies react with unrelated papillomavirus types, then the L1 protein is not conformationally correct (because conformational

epitopes are not conserved in unrelated HPV types).[1] While this assay method is not disclosed in the application, based on the disclosure and further based on what was known in the literature at the time of invention concerning the inherent type-specificity of conformational epitopes, one skilled in the art would have been aware that this would comprise a suitable method for confirming whether an expressed HPV L1 protein exhibits appropriate conformation.

Therefore, based on the foregoing, Applicants respectfully submit that, based on the teachings in this application and what was known in the art at the time of invention, one skilled in the art could practice the invention as it pertains to HPV-16. Therefore, withdrawal of the enablement rejection of Claims 10, 11, 15, 17, 18, 21, 22, 26, 51, 54 and 63 is respectfully requested.

Claims 1-3, 10-19, 21-26, 46, 47 and 50-63 further stand newly rejected under 35 U.S.C. §112, first paragraph. The Office Action asserts that the as-filed specification fails to provide support for expression of an L1 protein that reproduces the antigenicity of "intact, native human papillomavirus virus".

By the present amendment, the phrase "intact, native human papillomavirus virions" has been amended to --intact human papillomavirus virions--. As noted above, this language finds explicit support at page 10, lines 1-2 of the application.

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[1] It is known in the literature that a few conformational epitopes are conserved in highly related HPV's such as HPV-6 or HPV-11.

Therefore, withdrawal of the §112, first paragraph, rejection of Claims 1-3, 10-19, 21-26, 46, 47 and 50-63 is respectfully requested.

Finally, Claims 1-3, 10-19, 21-26, 46, 47 and 50-63 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. These claims are asserted to be indefinite in the recitation "native" and "mature". By the present amendments, "intact, mature human papillomavirus virions" has been amended to --intact human papillomavirus virions--. Thus, the §112, second paragraph, rejection should now be moot, because the meaning of an intact HPV virion would be readily apparent to one of ordinary skill in the art. Essentially, it refers to an infectious form of HPV. Withdrawal of the §112, second paragraph, rejection of Claims 1-3, 10-19, 21-26, 46, 47 and 50-63 is therefore respectfully requested.

Also, as disclosed at the interview, the undersigned again would like to bring to the attention of the Examiner several PCT applications (previously submitted) which have U.S. counterparts (one of which has matured into U.S. Patent No. 5,437,951). For the convenience of the Examiner, the cover page of the related patent as well as these PCT patent applications are attached to this Reply. The Examiner may wish to consider these documents in relation to a potential Interference.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding, the Examiner is respectfully requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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